**The current state of genetic risk models for the development of kidney cancer: a review and validation**

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Abstract

**Objective**

To review the current state of genetic risk models for predicting the development of kidney cancer, by identifying and comparing the performance of published models.

**Methods**

Risk models were identified from a recent systematic review and the Cancer-PRS web directory. A narrative synthesis of the models, previous validation studies and related genome-wide association studies (GWAS) was carried out. The discrimination and calibration of the identified models was then assessed and compared in the UK Biobank (UKB) cohort (cases = 452, controls=487,925).

**Results**

Thirty-nine genetic models predicting the development of kidney cancer were identified and thirty-one were validated in UKB. Several of the genetic-only models (n=7/25) and most of the mixed genetic-phenotypic models (n=5/6) had some discriminatory ability (area-under the receiver operating curve > 0.5) in this cohort. In general, models containing a larger number of genetic variants identified in GWAS performed better than models containing a small number of variants associated with known causal pathways. However, the performance of the included models was consistently poorer than genetic risk models for other cancers.

**Conclusions**

Although there is potential for genetic models to identify those at highest risk of developing kidney cancer, their performance is poorer than the best genetic risk models for other cancers. This may be due to the comparatively small number of genetic variants associated with kidney cancer identified in GWAS to date. The development of improved genetic risk models for kidney cancer is dependent on the identification of more variants associated with this disease. Whether these will have utility within future kidney cancer screening pathways is yet to be determined.

**Keywords**

Renal cell carcinoma, kidney cancer, genetics, risk models, risk stratification, polygenic risk scores, validation

Background

Recent developments in genetic research have led to the identification of hundreds of genetic variants associated with the development of different cancers [1]. Advances in sequencing technologies mean it is now possible to obtain genetic information from individuals at relatively low cost ($35 per individual [2]). Therefore, there is potential for genetic risk models, including polygenic risk scores (PRSs) that combine multiple single nucleotide polymorphisms (SNPs) together to estimate the risk of a disease or disease-related trait for an individual, to enhance risk prediction and improve the efficiency of population-level screening for cancer [2]. The BODICEA model for breast cancer, for example, which includes 313 SNPs alongside phenotypic risk factors, is already used to support clinical decision-making [2, 3] and studies are on-going to evaluate the role of this model within screening programs [4, 5].

There are several features of genetic risk models that will appeal to both clinicians and researchers. Firstly, germline genetic risk factors, including SNPs, do not change over the lifetime of an individual. This facilitates lifetime risk prediction rather than fixed time risk predictions (for example, the 5 or 10-year risk) and may help identify younger individuals at higher risk before the development of other risk factors. Secondly, genetic risk models do not rely on self-reporting and so are not at risk of recall or response bias. In the future, routine collection of genetic risk factors via a cheek swab or a pin-prick blood sample may be easier than the collection of other data. Thirdly, genetic factors are largely independent of, and hence complimentary to, other risk factors [2]. Consequently, genetic risk models, unlike many phenotypic models, do not predispose towards older and sicker people [6]. There is also evidence, from a recent population-based survey, that genetic risk models would be more acceptable to the general public than risk scores which use lifestyle risk factors, in the context of risk-stratified screening for cancer [7].

The potential for genetic risk models to enhance disease risk prediction is appealing in the context of kidney cancer. A lack of symptoms, even at late stages of the disease, makes the detection of kidney cancer a challenge: 60% of kidney cancers in the UK are currently diagnosed incidentally and around 20% of those are late stage (III-IV) at diagnosis with associated poor five-year cancer specific survival rates (6% for stage IV) **[8]**. Together with the observed increase in incidence of kidney cancer [9], this has led to international interest in the potential for a screening programme **[10]. However, as the incidence of kidney cancer is relatively low in the general population [11], a targeted, risk-stratified approach - using risk models to identify high-risk individuals most likely to benefit from screening - is likely to be necessary [12, 13].** Risk models could also be used to guide choice of screening test and may provide opportunities for risk reduction interventions. In a previous validation study [14], we demonstrated that phenotypic risk models (incorporating lifestyle and demographic risk factors) that predict the development of kidney cancer have reasonable performance (95% confidence intervals of the area-under the receiver operating characteristic curve (AUROC): 0.50-0.71). However, the modelled incremental benefit over age was small. Adding genetic risk factors to phenotypic risk models has been shown to increase the discriminatory ability for other cancers [15].

In this review we identify and evaluate existing models that both predict the development of kidney cancer and include genetic risk factors (either alone or in combination with other risk factors) to provide an overview of the current state of research in this area. We also assess the performance of the identified risk models in a large UK population (the UK Biobank (UKB) cohort) to enable a comparison between the included models and with genetic risk models for other cancers. A glossary of terms is provided in Box 1.

Methods

We identified risk models from a recent systematic review [16] and the Cancer-PRS web directory (an online repository for polygenic risk scores for major cancer traits) [17]. We extracted data on the genetic risk factors (including how they were identified), the performance of the models in external validation studies and any comparisons to risk scores for other cancers.

The performance of the models was then assessed in the UKB cohort, a large population based cohort of around 500,000 individuals aged 40-69 enrolled between 2006 and 2010 [18]. All participants attended a baseline assessment that included completion of questionnaires about lifestyle and medical history and measurement of a range of physical characteristics. Data on cancer incidence is available for UKB participants through linkage to national cancer registries. Full genotype information is available for 488,377 members of UKB (see supplementary methods). To maximise the number of cases, a closed-cohort analysis with 6-years of follow-up was used for the validation. Cases of kidney cancer (all types) were included if they occurred within 6-years of baseline assessment. Individuals with a diagnosis of kidney cancer prior to baseline (n=452) were excluded from the analysis.

Two of the models included in this review, Fritsche et al. (2020) [17], uses SNPs that were originally identified as having an association with kidney cancer in a genome-wide association study (GWAS) that used the UKB cohort. Therefore, the results presented for the Fritsche et al. (2020) models cannot be considered true external validation. None of the other models used the UKB cohort as a development cohort or used SNPs identified in a GWAS that used the UKB cohort.

The performance, both discrimination and calibration, was measured for all of the models included in the validation. Discrimination was measured using the area under the receiver-operating curve (AUROC) and the mean standardised score (MSS). Calibration was assessed graphically in deciles (see Supplementary methods). For models with sufficient unique values, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the deciles of the population with the highest and lowest scores.

A complete case approach was used for the primary analysis; each model was only computed for individuals with data for all of the risk factors used in that model. As this done on a model-by-model basis, the cohort size varies slightly for each validation. Any phenotypic variables with more than 5% missing data were multiply imputed using a predictive mean matching approach (see supplementary methods). Several sensitivity analyses were carried out; including stratified analyses to determine variation in performance by sex and ethnicity (see supplementary methods).

Results

Twenty-two studies describing 39 models that predict the risk of kidney cancer using genetic risk factors were identified and included in the narrative synthesis [15, 17, 19-38].

***Genetic Risk Factors***

Ninety genetic variants (SNPs) are used in the 39 models. The number of SNPs included in each models ranges from one (combined with other risk factors in a mixed genetic-phenotypic models [21, 27, 28, 30]) to 19 [15, 26]. Details of the variables (including SNPs) used in each model are given in Table 1. Most of the SNPs (n=63) are only used in a single study, however, the remainder SNPs (n=27) are implemented in models developed in more than one study. The most commonly used SNPs (rs2241261, rs11813268, rs10936602, rs74911261, rs4381241, rs718314) were used in models from six different studies. Further details of the SNPs used (including effect allele, MAF and imputation score in UKB) are given in Table S7.

Most of the SNPs included in the models were relatively common variants within the UKB cohort, with only seven rare alleles (a minor allele fraction (MAF) less than 5%) identified. In particular, we note the models developed by Lin et al. [31], Fritsche et al. (2018) [25] and Fritsche et al. (2020) [17] which all used more than one rare allele (MAF <%5) in their respective models.

Most of the included studies (n=14), including all of those published prior to 2017, selected small numbers of SNPs of interest to include in models, based on known causalpathways for renal cell carcinoma [19-24, 27, 28, 30, 31, 35-38]. Variants on genes associated with vitamin D activity [19], immunoregulatory responses [22], susceptibility to stress [23], telomere length [24], DNA repair [28], adiponectin levels [27], the mTOR (mammalian target of rapamycin) pathway [35] and miRNA binding sites [36, 37] were all included by different studies based on hypothesised associations with kidney cancer. Additionally, genes with known associations to carcinogenesis [20], solid cancers [21], kidney cancer [30] and renal cell carcinoma (RCC) [38] were selected by four of these studies.

Eight of the included studies, all published since 2017, used SNPs found to be associated with kidney cancer in genome-wide association studies (GWAS) [15, 17, 25, 26, 29, 32-34]. In GWAS, the whole genome of a large cohort is searched for association to the outcome of interest. This approach can identify large numbers of genetic variants, but biological mechanisms linking the identified SNPs to the outcome are not identified. Nine separate GWAS were given as sources for SNPs used in models included in this review, see Table 4 [33, 39-46]. Most (n=7) used RCC as the outcome for which associations were identified [33, 39-43, 45], while one used the outcome of Wilm’s tumour [44] and one did not report the outcome [46]. The size of the GWAS populations ranged from 2636 [44] to 408961 (the UKB cohort) [46], with the number of outcomes ranging from 757 [44] to 10784 [33]. All of these GWAS except one [33], exclusively used white (often defined as European ancestry) populations.

***Genetic Risk Models***

We identified 14 studies (describing 27 models) that used SNPs located in genes associated with known causal pathways for kidney cancer [19-24, 27, 28, 30, 31, 35-38]. All of these studies used a case-control design to develop models and most recruited patients with RCC as cases (Table S2). Furthermore, they all recruited majority male populations (57%-85%) with a mean age >50 years. A range of ethnicities are represented, including Asian (n=8) [19-22, 27, 28, 36, 38], white-only (n=4) [23, 31, 35] and mixed ethnicity (n=1) [30]. The development populations range in size from 355 (100 cases, 225 controls) [36] to 2050 (894 cases, 1156 controls) [37]. The number SNPs included in these models ranges from 1 to 12 (Table 1). Only one study (Wu et al. [38]) reported the discrimination of any of these models in their development population, and to the knowledge of the authors there have been no prior external validations of these models. Thirteen of these models included phenotypic risk factors alongside genetic factors [19, 21, 24, 27, 28, 30]. The most common included risk factors in the mixed models are smoking (n=10), sex (n=9), BMI (n=9), age (n=8), and hypertension (n=8).

A further eight studies (12 models) combine SNPs identified through GWAS (8 studies and 12 models) [15, 17, 25, 26, 29, 32-34]. Both the SNPs and their weighting are determined in GWAS and then compiled to form a polygenic risk score (PRS). The number of SNPs used in these models ranges from 7 to 19.

***Published Performance of Genetic Risk Models***

Eight of the genetic-only risk models included in this review have previously validated in external populations [15, 17, 25, 26, 29, 34]. In most of these validations, the genetic model for kidney cancer is shown to have some ability to distinguish individuals at high risk (see Table S3).

In the study by Kachuri et al. [15], the predictive value of adding a cancer-specific PRS to a phenotypic model (including age, family history and modifiable lifestyle risk factors) is also evaluated. The discrimination, measured by the c-index, for the kidney cancer model increased from 0.716 to 0.723 when adding the PRS to the model. The authors estimate that the population attributable fraction (PAF) for the genetic risk factors included in their model is 4.6%.

All of the external validation studies used populations from the UK and USA and all limited to either European ancestry [15, 17, 25, 26, 29], Caucasians [34] or self-reported white individuals [17]. Additionally, all use kidney cancer (all types, excluding renal cancer of the pelvis), not RCC, as the outcome of interest.

***Comparable performance of genetic risk models***

We validated 31 of the identified models in the UKB cohort [15, 17, 20-26, 29-38]. Eight models were not validated either because some of the variables included were not available for the UKB cohort [27, 28] or because the information required to validate the models was not available [19].

We included 438,315 individuals from the UKB cohort, including 620 cases of kidney cancer, in the primary analysis (Table 2). In this cohort, the six genetic-only models with the highest discrimination (all with adequate calibration), used SNPs derived from GWAS [15, 26, 29, 33, 34] (Fig. 1). Of these, the polygenic risk score by Scelo et al. [29] had the highest discrimination (AUROC=0.551 (95% CI: 0.528-0.573)). This model also has the highest odds ratio per standard deviation of risk score, 1.189 (se: 0.051). The Scelo et al. model is adequately calibrated; with some overestimation in the high-risk deciles (see supplementary materials for plots). The genetic-only models with the highest sensitivity (14.3%) and PPV (0.20%) for the 10% of the population with the highest scores are the two developed by Shi et al. [34], which use 10 SNPs weighted for the development and validation populations respectively (Table S5). The model developed by Jia et al. [29], which includes 15 SNPs, has the lowest sensitivity (6.7%) and PPV (0.094%) for the 10% of the population with the lowest scores. Of the genetic-only models using variants inferred from a causal pathway, only the model developed by Verma et al. [36] – which used SNPs from miRNA genes previously shown to be associated with solid cancers - had discriminative ability (AUROC=0.526 (95% CI: 0.504-0.549)), however, calibration is poor. No other genetic-only models showed discriminative ability (Table 2, Fig. 1). In general, the discrimination of the genetic-only models improves as more SNPs are added to the models (Fig. 2).

Five of the six mixed phenotypic-genetic models included in the validation showed discriminative ability (lower bound of the AUROC > 0.5) [21, 30] (Table 3, Fig. 1). Of these, the best performing are the three models developed by Li et al. [30] that all combine a single SNP (from the APOE promoter region) with seven phenotypic risk factors, including age and smoking, (95% confidence interval range of the AUROC: 0.584-0.636, calibration: adequate, underestimation by the model in high-risk deciles).

The supplementary analyses revealed no clear difference in discrimination between men and women or between the entire cohort and white-only members of UKB. When removing one of each set of third-degree relatives from the cohort, the six highest performing genetic-only models [15, 26, 29, 33, 34] have no significant differences in discrimination (95% confidence interval of the AUROCs: 0.510-0.571), suggesting that in unrelated individuals these six models would be expected to have similar performance. The results from all sensitivity analyses can be found in supplementary materials.

Note that at least two of the models validated in this study, developed by Fritsche et al. (2020) [17], use SNPs identified in GWAS of the UKB cohort (see Table 4). There have also been previously reported external validations of several of the models that have used the UKB cohort (see Table S3) [15, 17, 26, 29]. The results of this study are in agreement with these previous validations.

***Comparable performance of kidney genetic risk models to genetic risk models for other cancers***

Several of the included validation studies reported the performance of kidney cancer risk models in comparison to risk models for other cancers in the same cohort. Compared to the best performing genetic only models for other types of cancer, the performance of the kidney cancer genetic models is relatively poor. In four of the six identified validation studies [15, 17, 25, 29], the kidney cancer model has the lowest or second lowest performance of all the cancer-specific genetic risk scores evaluated. In most of these validations, the kidney cancer model is outperformed by models for more common cancers with a greater number of associated SNPs (including breast, prostate and colorectal – but not lung). For example, in a study by Jia et al. [29], they report that individuals with the highest 5% (cancer-specific) PRS have a 2-3 times elevated risk of cancer of the prostate, breast, pancreas, colorectal and ovary, but only a 1.5 times elevated risk for lung, bladder or kidney cancer. In their validation, the genetic risk model (included in this review) for kidney cancer had the lowest AUROC value of the eight cancer types examined. In the validation of genetic risk models for 16 types of cancer by Kachuri et al. [15], the increase in discrimination observed when adding a genetic risk score (included in this review) to models with other risk factors for kidney cancer (c-index 0.716 to 0.723) is also the second lowest of the included cancer types. The increase in discrimination is much lower than for breast cancer (where the c-index increased from 0.572 to 0.635) but comparable to that seen for bladder cancer (where the c-index increased from 0.808 to 0.814). The PAF for the genetic risk included in the kidney cancer model (4.6%) is also lower than seen for bladder cancer (8.5%) or colorectal cancer (16.8%). In other validations, however, the kidney cancer model performs adequately compared to genetic models for other cancers. In Graff et al. [26], the kidney cancer model (included in this review) ranks 11th out of 15th evaluated, with an effect size per standard deviation (OR: 1.21, (1.14-1.26)) higher than four other scores, including the PRS for oral cancer (OR: 1.08, (1.02-1.14)) and the PRS for lung cancer (OR: 1.12, (1.08-1.17)).

Discussion

In this review, we have identified all existing models that use genetic risk factors that predict the risk of developing kidney cancer, and then validated the majority in the UK Biobank cohort. At least 39 risk models incorporating 90 different genetic variants have been developed to predict the risk of kidney cancer. Several genetic-only risk models demonstrate potential to discriminate between those at higher and lower risk of kidney cancer (lower bound of the AUROC>0.5). However, the best performing genetic-only model has an AUROC value of 0.551 (95% CI: 0.528-0.573) [33], considerably lower than the AUROC seen for genetic-only risk models in some other cancers. The incremental benefit of adding a genetic risk model for kidney cancer to a phenotypic risk model is also marginal (an increase in AUROC of 0.007 from 0.716 (se: 0.011) to 0.723 (se: 0.011)), and lower than observed for other cancers (the AUROC increases by 0.063 from 0.572 (se: 0.005) to 0.635 (se: 0.004) for breast cancer) [15].

The performance of the kidney cancer models in UKB also compares poorly with genetic risk models for other cancers validated in UKB. For example, the genetic model developed by Huyghe et al. [47] for colorectal cancer has a AUROC value of 0.63 (95% CI, 0.61-0.64) [48] and the model developed by Mavaddat el al. [49] for breast cancer has an AUROC value of 0.63 (95% CI, 0.63-0.65) in a validation cohort of women (largely drawn from UKB).

Two observations suggest that the comparatively poor performance of current genetic risk models for predicting kidney cancer is probably due to the limited number of SNPs currently identified and included within the models. Firstly, the number of SNPs included in the kidney cancer models is considerably lower than for other cancers. In Graff et al. [26], 19 SNPs are included in the kidney cancer model (the highest number of any model included in this review), whereas in the same study 103 and 187 SNPs are used in the scores for colorectal and breast cancer respectively. Further, the analysis in this review suggests that discrimination improves as the number of SNPs increases (Fig. 2). This has been seen in other cancers, for example, in a previous validation of genetic risk models for colorectal cancer (also in UKB) models with similar numbers of SNPs - Yarnall 2013 (15 SNPs) and Ibanez-Sanz 2017 (23 SNPs) - have comparable performance (AUROCs of 0.56 (95% CI: 0.54-0.57) and 0.56 (95% CI: 0.54-0.58)) to the Graff model (19 SNPs) for kidney cancer. The best performing model (Huyghe et al. [47]) from that validation of includes 120 SNPs and has an AUROC of 0.63 (95% CI, 0.61-0.64).

Secondly, the PAF for one of the best genetic-only risk models for kidney cancer included in this review (Kachuri et al., 19 SNPs) is estimated to be only 4.6% [15]. However, a study of environmental and heritable risk, using a large Nordic cohort of twins, estimates that the true PAF of genetic risk factors for kidney cancer could be as high as 38% [50]. Similarly, a 2015 study found that that the genetic variants identified by GWAS (at that time) explained only 14.7% of the heritability associated with kidney cancer [51]. This suggests that there may be up to 100 SNPs associated with kidney cancer risk that have not yet been identified.

The limited number of SNPs identified to date is likely due to the relatively small number of GWAS for kidney cancer. Compared with the nine GWAS studies used to develop kidney cancer risk models [33, 39-46], there have been over 100 different breast cancer GWAS [52]. If the potential for genetic risk models for kidney cancer is going to be realised, there is a need for further GWAS studies to identify as of yet unknown variants associated with the development of this disease. Given the relatively low prevalence of kidney cancer (0.17 (95%CI:0.09-0.27), in Europe [11]), larger cohort sizes or longer follow-up periods than studies for more common cancers will likely be needed to include sufficient case numbers in the analysis.

Alongside these efforts to identify further SNPs, there are also a number of other areas that need considering before any of these genetic risk models can be incorporated into clinical practice. Perhaps the most significant is the lack of data from individuals of non-white ethnicity. Given the small numbers of individuals who self-report non-white ethnicity in UKB, it was not possible to conduct analyses stratified by ethnicity in the validation performed in this review. The best performing genetic models use SNPs identified in GWAS that included used almost exclusively white-only populations (see Table S3) and all previous external validations have excluded all non-white individuals from their analyses (see Table S2). The performance of these models across different ethnic groups is, therefore, a key question for this area of research. This is not unique to kidney cancer, a lack of ethnically diverse populations is a challenge across the field of genetics [53], with nearly 80% of individuals included in published GWAS being of European descent [54]. There is an urgent need for the prioritisation of genetic data generation from individuals from under-represented ethnic groups (including African and Asian ancestries) [2]. Other considerations common across all cancers include how best to collect, store and share genetic data [55], how to communicate the results of genetic risk scores to individuals to minimise any psychosocial harms, how to address the training needs of healthcare professionals and the need for clear regulatory frameworks to ensure responsible and equitable use of genetic risk models [2]. Modelling and cost-effectiveness analyses are also needed to assess the potential benefits of incorporating genetic-risk based stratification within the specific context of potential kidney cancer screening programmes, once a suitable model had been developed.

Although it is encouraging to see the potential for genetic risk models to predict the development of kidney cancer, their relatively weak performance leads us to conclude that this area of research is not yet ready for transition into clinical practise. The low discrimination of even the best models included in this validation, means that they would not be as good as existing phenotypic models at selecting high-risk individuals for screening. Although there has been rather limited research into combining genetic and phenotypic models for kidney cancer, the recent study showing that the Kachuri genetic model only marginally improved the performance of a phenotypic model is not promising [15]. Without compelling evidence that the use of a genetic model could lead to a significantly better selection of high-risk individuals, the additional expense and burden of collecting genetic information cannot be justified.

***Conclusions***

While 90 genetic risk factors have been included in nearly 40 published genetic models predicting the risk of the development of kidney cancer, only a small number of these show any discriminative ability and the addition of genetic risk to phenotypic risk models results in only marginal improvement [15].

Overall, the best genetic models for kidney cancer perform poorly compared to the best genetic models developed for other cancers. Estimates suggest that the currently identified SNPs account for only 10-20% of hereditable risk for kidney cancer. This may be due to the relatively small number of GWAS studies carried out for kidney cancer outcomes compared with those for other cancers, and hence, the relatively small number of variants associated with kidney cancer that have been identified.

Therefore, although in principle it is possible to identify individuals at higher risk of kidney cancer using existing models, these models are unlikely to have utility within clinical practice. If more large GWAS studies are conducted and more variants associated with kidney cancer are identified it seems likely that the development of higher performing PRSs will be achievable. Whether these will have utility within future kidney cancer screening pathways is yet to be determined. On-going research in other disease areas is also needed to ensure the responsible and equitable use of genetic risk scores in this context [2].

Box 1: Glossary of Terms

SNP (single nucleotide polymorphism) – the most common type of genetic variation, SNPs refer to the difference of a nucleotide in a specific location in DNA (e.g. the replacement of the nucleotide cytosine (C) with the nucleotide thymine (T))

GWAS (genome wide association studies) – A genome-wide association study is an approach that involves scanning markers across complete sets of DNA of many individuals to find SNPs associated with a particular disease.

Discrimination (of a risk model) - a measure of how well a prediction model distinguishes between individuals with and without the outcome of interest. A model with discriminative ability will, on average, assign higher risk to the cases than the controls.

Calibration (of a risk model) - a measure of the agreement between the predicted and observed outcomes, the risk predicted by a model and observed risk.

AUROC (area under the receiver operating characteristic) curve - A receiver operating characteristic curve plots the sensitivity against 1-specificity for a range of cut-off points. The area under the curve is equal to the probability that an individual with the outcome is assigned a higher risk than a randomly chosen control. An AUROC value of 1.0 indicates a model with perfect discriminative ability, a value of 0.5 indicates discrimination no better than random assignment. Harrell’s concordance index (c-index) is an equivalent measure used in open cohort (e.g. survival) analysis.

Population attributable fraction (PAF) – a widely used epidemiological measure of the fraction of all cases of a particular disease or other adverse condition in a population that is attributable to a specific exposure. This can be interpreted as the proportion of cases that would not have occurred if the exposure was not present.

Phenotypic – the observable characteristics of an individual resulting from the interaction of their genome with the environment. In this review, we refer to phenotypic models that may include demographic, lifestyle and clinical risk factors.

PRS (polygenic risk scores) – also referred to as genome-wide scores or genetic risk scores summarise the estimated effect of many genetic variants (SNPs) on an individual. Here we specifically use the term PRS to refer to models constructed from weights derived from a GWAS.

Cancer PRS web directory – an online repository for polygenic risk scores for major cancer traits https://prsweb.sph.umich.edu:8443/

Germline mutations – mutations or variation association that are present in germ cells and can be passed on to offspring (as opposed to somatic mutations that occur outside of germline cells and cannot be passed on to offspring).

Truncating variants –a genetic variation that results in a shorter version of the associated protein being expressed, which can cause loss of function for the gene in which they are present.

Minor allele fraction (MAF) – the proportion at which the second most common allele occurs in a given population. Common variants are considered to be those with a MAF > 5% (although a cut-off of >1% is not uncommon). Rare variants, while they can confer a high risk, will only be present in a small number of the cases and therefore will have little effect on the overall predictive accuracy of the model.

Box 2: Key Papers

Kachuri, L., Graff, R.E., Smith-Byrne, K., et al., *Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction.* Nature Communications, 2020. **11**(1): p. 6084.

Scelo, G., Purdue, M.P., Brown, K.M., et al., *Genome-wide association study identifies multiple risk loci for renal cell carcinoma.* Nature Communications, 2017. **8**: p. 15724.

Jia, G., Lu, Y., Wen, W., et al., *Evaluating the Utility of Polygenic Risk Scores in Identifying High-Risk Individuals for Eight Common Cancers.* JNCI Cancer Spectrum, 2020. **4**(3).

Mucci, L.A., Hjelmborg, J.B., Harris, J.R., et al., *Familial Risk and Heritability of Cancer Among Twins in Nordic Countries.* Jama, 2016. **315**(1): p. 68-76.

Ethics Statement

The UK Biobank study was approved by the North West Multi- Centre Research Ethics

Committee (reference number 06/MRE09/ 65), and at recruitment all participants gave

informed written consent to participate in UK Biobank and be followed up, using a signature

capture device.

Conflicts of Interest

GDS has received educational grants from Pfizer, AstraZeneca and Intuitive Surgical; consultancy fees from Pfizer, Merck, EUSA Pharma and CMR Surgical; Travel expenses from Pfizer and Speaker fees from Pfizer. All other authors have no financial disclosures.

Funding Statement

HH was supported by a National Institute of Health Research Development and Skills Enhancement Award (NIHR301182) and is now supported by an International Alliance for Cancer Early Detection Project Award (ACEDFR3\_0620I135PR007). SHR is supported by The Urology Foundation and a Cancer Research UK Clinical Research Fellowship. GDS’s work on this topic is funded by Kidney Cancer UK, The Urology Foundation, The Rosetrees Trust, Yorkshire Cancer Research and Cancer Research UK and supported by The Mark Foundation for Cancer Research, the Cancer Research UK Cambridge Centre [C9685/A25177] and NIHR Cambridge BRC. The University of Cambridge has received salary support in respect of SJG from the NHS in the East of England through the Clinical Academic Reserve. JUS was funded by a Cancer Research UK Prevention Fellowship (C55650/A21464) and is now supported by a National Institute of Health Research Advanced Fellowship (NIHR300861). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

1. Sud, A., Kinnersley, B., and Houlston, R.S., *Genome-wide association studies of cancer: current insights and future perspectives.* Nature Reviews Cancer, 2017. **17**(11): p. 692-704.

2. *Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps.* Nat Med, 2021. **27**(11): p. 1876-1884.

3. Lee, A., Mavaddat, N., Wilcox, A.N., et al., *BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors.* Genetics in medicine : official journal of the American College of Medical Genetics, 2019. **21**(8): p. 1708-1718.

4. Brooks, J.D., Nabi, H.H., Andrulis, I.L., et al., *Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I).* J Pers Med, 2021. **11**(6).

5. Shieh, Y., Eklund, M., Madlensky, L., et al., *Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial.* J Natl Cancer Inst, 2017. **109**(5).

6. Tammemägi, M.C., Ruparel, M., Tremblay, A., et al., *USPSTF2013 versus PLCOm2012 lung cancer screening eligibility criteria (International Lung Screening Trial): interim analysis of a prospective cohort study.* The Lancet Oncology, 2021.

7. Usher-Smith, J.A., Harvey-Kelly, L.L.W., Rossi, S.H., et al., *Acceptability and potential impact on uptake of using different risk stratification approaches to determine eligibility for screening: A population-based survey.* Health Expect, 2021. **24**(2): p. 341-351.

8. Vasudev, N.S., Wilson, M., Stewart, G.D., et al., *Challenges of early renal cancer detection: symptom patterns and incidental diagnosis rate in a multicentre prospective UK cohort of patients presenting with suspected renal cancer.* BMJ Open, 2020. **10**(5): p. e035938.

9. Cancer Research UK. *Kidney Cancer Statistics*. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer> [Accessed: 12/10/2018]

10. Usher-Smith, J., Simmons, R.K., Rossi, S.H., and Stewart, G.D., *Current evidence on screening for renal cancer.* Nat Rev Urol, 2020.

11. Rossi, S.H., Hsu, R., Blick, C., et al., *Meta-analysis of the prevalence of renal cancer detected by abdominal ultrasonography.* BJS, 2017. **104**(6): p. 648-659.

12. Meisel, S.F., Side, L., Fraser, L., et al., *Population-Based, Risk-Stratified Genetic Testing for Ovarian Cancer Risk: A Focus Group Study.* Public Health Genomics, 2013. **16**(4): p. 184-191.

13. Pashayan, N., Morris, S., Gilbert, F.J., and Pharoah, P.D.P., *Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model.* JAMA Oncol, 2018. **4**(11): p. 1504-1510.

14. Harrison, H., Pennells, L., Wood, A., et al., *Validation and Public Health Modelling of Risk Prediction Models for Kidney Cancer using UK Biobank.* BJU Int, 2021.

15. Kachuri, L., Graff, R.E., Smith-Byrne, K., et al., *Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction.* Nature Communications, 2020. **11**(1): p. 6084.

16. Harrison, H., Thompson, R.E., Lin, Z., et al., *Risk Prediction Models for Kidney Cancer: A Systematic Review.* Eur Urol Focus.

17. Fritsche, L.G., Patil, S., Beesley, L.J., et al., *Cancer PRSweb: An Online Repository with Polygenic Risk Scores for Major Cancer Traits and Their Evaluation in Two Independent Biobanks.* Am J Hum Genet, 2020. **107**(5): p. 815-836.

18. Allen, N., Sudlow, C., Downey, P., et al., *UK Biobank: Current status and what it means for epidemiology.* Health Policy Technol, 2012. **1**(3): p. 123-126.

19. Arjumand, W., Ahmad, S.T., Seth, A., Saini, A.K., and Sultana, S., *Vitamin D receptor FokI and BsmI gene polymorphism and its association with grade and stage of renal cell carcinoma in North Indian population.* Tumor Biology, 2012. **33**(1): p. 23-31.

20. Chang, W.S., Tsai, C.W., Wang, S.M., et al., *Association of caveolin-1 genotypes with renal cell carcinoma risk in Taiwan.* The Chinese journal of physiology, 2014. **57**(4): p. 220-226.

21. Chen, J., Cheng, M., Yi, L., and Jiang, C.B., *Relationship between CYP1A1 genetic polymorphisms and renal cancer in China.* Asian Pacific Journal of Cancer Prevention: Apjcp, 2011. **12**(9): p. 2163-6.

22. Chu, H., Wang, M., Yan, F., et al., *Polymorphisms in the IL-13 and IL-4r genes are associated with the development of renal cell carcinoma.* Annals of Oncology, 2012. **23**(8): p. 2114-2121.

23. Coric, V.M., Simic, T.P., Pekmezovic, T.D., et al., *GSTM1 genotype is an independent prognostic factor in clear cell renal cell carcinoma.* Urologic Oncology: Seminars and Original Investigations, 2017. **35**(6): p. 409-417.

24. de Martino, M., Taus, C., Lucca, I., et al., *Association of human telomerase reverse transcriptase gene polymorphisms, serum levels, and telomere length with renal cell carcinoma risk and pathology.* Molecular Carcinogenesis, 2016. **55**(10): p. 1458-66.

25. Fritsche, L.G., Gruber, S.B., Wu, Z., et al., *Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-wide Study: Results from The Michigan Genomics Initiative.* Am J Hum Genet, 2018. **102**(6): p. 1048-1061.

26. Graff, R.E., Cavazos, T.B., Thai, K.K., et al., *Cross-cancer evaluation of polygenic risk scores for 16 cancer types in two large cohorts.* Nature Communications, 2021. **12**(1): p. 970.

27. Hsueh, Y.M., Chen, W.J., Lin, Y.C., et al., *Adiponectin gene polymorphisms and obesity increase the susceptibility to arsenic-related renal cell carcinoma.* Toxicology and Applied Pharmacology, 2018. **350**: p. 11-20.

28. Hsueh, Y.M., Lin, Y.C., Chen, W.J., et al., *The polymorphism XRCC1 Arg194Trp and 8-hydroxydeoxyguanosine increased susceptibility to arsenic-related renal cell carcinoma.* Toxicology and Applied Pharmacology, 2017. **332**: p. 1-7.

29. Jia, G., Lu, Y., Wen, W., et al., *Evaluating the Utility of Polygenic Risk Scores in Identifying High-Risk Individuals for Eight Common Cancers.* JNCI Cancer Spectrum, 2020. **4**(3).

30. Li, Y. and Graubard, B.I., *Pseudo semiparametric maximum likelihood estimation exploiting gene environment independence for population-based case-control studies with complex samples.* Biostatistics, 2012. **13**(4): p. 711-723.

31. Lin, J., Pu, X., Wang, W., et al., *Case-control analysis of nucleotide excision repair pathway and the risk of renal cell carcinoma.* Carcinogenesis, 2008. **29**(11): p. 2112-2119.

32. Machiela, M.J., Hofmann, J.N., Carreras-Torres, R., et al., *Genetic Variants Related to Longer Telomere Length are Associated with Increased Risk of Renal Cell Carcinoma.* European Urology, 2017. **72**(5): p. 747-754.

33. Scelo, G., Purdue, M.P., Brown, K.M., et al., *Genome-wide association study identifies multiple risk loci for renal cell carcinoma.* Nature Communications, 2017. **8**: p. 15724.

34. Shi, Z., Yu, H., Wu, Y., et al., *Systematic evaluation of cancer-specific genetic risk score for 11 types of cancer in The Cancer Genome Atlas and Electronic Medical Records and Genomics cohorts.* Cancer Medicine, 2019. **8**(6): p. 3196-3205.

35. Shu, X., Lin, J., Wood, C.G., Tannir, N.M., and Wu, X., *Energy balance, polymorphisms in the mTOR pathway, and renal cell carcinoma risk.* Journal of the National Cancer Institute, 2013. **105**(6): p. 424-32.

36. Verma, A., Singh, V., Jaiswal, P., and Mittal, R.D., *Genetic Variants in miRNAs Associated with Renal Cell Carcinoma (RCC) Risk: A Pilot Study in North Indian Population.* Indian Journal of Clinical Biochemistry, 2015. **30**(4): p. 386-393.

37. Wei, H., Ke, H.L., Lin, J., et al., *MicroRNA target site polymorphisms in the VHL-HIF1alpha pathway predict renal cell carcinoma risk.* Molecular Carcinogenesis, 2014. **53**(1): p. 1-7.

38. Wu, Y., Zhang, N., Li, K., et al., *Genetic scores based on risk-associated single nucleotide polymorphisms (SNPs) can reveal inherited risk of renal cell carcinoma.* Oncotarget, 2016. **7**(14): p. 18631-18637.

39. Gudmundsson, J., Sulem, P., Gudbjartsson, D.F., et al., *A common variant at 8q24.21 is associated with renal cell cancer.* Nat Commun, 2013. **4**: p. 2776.

40. Han, S.S., Yeager, M., Moore, L.E., et al., *The chromosome 2p21 region harbors a complex genetic architecture for association with risk for renal cell carcinoma.* Hum Mol Genet, 2012. **21**(5): p. 1190-200.

41. Henrion, M., Frampton, M., Scelo, G., et al., *Common variation at 2q22.3 (ZEB2) influences the risk of renal cancer.* Human molecular genetics, 2013. **22**(4): p. 825-831.

42. Henrion, M.Y., Purdue, M.P., Scelo, G., et al., *Common variation at 1q24.1 (ALDH9A1) is a potential risk factor for renal cancer.* PLoS One, 2015. **10**(3): p. e0122589.

43. Purdue, M.P., Johansson, M., Zelenika, D., et al., *Genome-wide association study of renal cell carcinoma identifies two susceptibility loci on 2p21 and 11q13.3.* Nat Genet, 2011. **43**(1): p. 60-5.

44. Turnbull, C., Perdeaux, E.R., Pernet, D., et al., *A genome-wide association study identifies susceptibility loci for Wilms tumor.* Nat Genet, 2012. **44**(6): p. 681-4.

45. Wu, X., Scelo, G., Purdue, M.P., et al., *A genome-wide association study identifies a novel susceptibility locus for renal cell carcinoma on 12p11.23.* Human molecular genetics, 2012. **21**(2): p. 456-462.

46. Zhou, W., Nielsen, J.B., Fritsche, L.G., et al., *Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies.* Nat Genet, 2018. **50**(9): p. 1335-1341.

47. Huyghe, J.R., Bien, S.A., Harrison, T.A., et al., *Discovery of common and rare genetic risk variants for colorectal cancer.* Nature Genetics, 2019. **51**(1): p. 76-87.

48. Saunders, C.L., Kilian, B., Thompson, D.J., et al., *External validation of risk prediction models incorporating common genetic variants for incident colorectal cancer using UK Biobank.* Cancer Prevention Research, 2020: p. canprevres.0521.2019.

49. Mavaddat, N., Michailidou, K., Dennis, J., et al., *Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes.* The American Journal of Human Genetics, 2019. **104**(1): p. 21-34.

50. Mucci, L.A., Hjelmborg, J.B., Harris, J.R., et al., *Familial Risk and Heritability of Cancer Among Twins in Nordic Countries.* Jama, 2016. **315**(1): p. 68-76.

51. Sampson, J.N., Wheeler, W.A., Yeager, M., et al., *Analysis of Heritability and Shared Heritability Based on Genome-Wide Association Studies for Thirteen Cancer Types.* J Natl Cancer Inst, 2015. **107**(12): p. djv279.

52. Yanes, T., Young, M.-A., Meiser, B., and James, P.A., *Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field.* Breast Cancer Research, 2020. **22**(1): p. 21.

53. Peterson, R.E., Kuchenbaecker, K., Walters, R.K., et al., *Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations.* Cell, 2019. **179**(3): p. 589-603.

54. Sirugo, G., Williams, S.M., and Tishkoff, S.A., *The Missing Diversity in Human Genetic Studies.* Cell, 2019. **177**(1): p. 26-31.

55. Aronson, S.J. and Rehm, H.L., *Building the foundation for genomics in precision medicine.* Nature, 2015. **526**(7573): p. 336-42.